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X-Linked Microcephaly, Microphthalmia, Microcornea, Congenital Cataract, Hypogenitalism, Mental Deficiency, Growth Retardation, Spasticity: Possible New Syndrome

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We describe a male and his sister's son with microcephaly, microphthalmia, microcornea, congenital cataract, hypogenitalism, severe mental deficiency, progressive spasticity and growth retardation. Both affected males have brachycephaly, upslanting palpebral fissures, epicanthal folds, highly arched palate, small mouth, and retrognathia. Two maternal cousins of the propositus's mother may also have been affected. Chromosomal and metabolic findings in the propositus were normal. To our knowledge, this disorder had not been reported before as an X-linked syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: X-linked inheritance, hypogonadism, mild dysmorphic facial features

INTRODUCTION

Microcephaly, microphthalmia, congenital cataract, mental deficiency, hypogenitalism, growth retardation are described as components of several genetic syndromes [Smith et al., 1964; Martsolf et al., 1978; Frydman et al., 1985] which are autosomal recessive traits. The combination of microcephaly, microphthalmia, cataract, mental deficiency, spasticity, hypogenitalism, and growth retardation with normal metabolic screening finding has, according to our knowledge, not been reported before as X-linked disorder.

We report on 2 males, related as nephew and maternal uncle, affected with a combination of these anomalies. The facial changes were minor anomalies and it seems unlikely that there is an easily recognizable pattern; nevertheless, they both have had a similar appearance. Two maternal cousins of the mother of the propositus could also be affected. We conclude that our patients represent a new X-linked multiple congenital anomalies and mental retardation disorder.

CLINICAL REPORTS

Patient 1

The propositus IV-2 (Fig. 1), a 6-year-old boy (Fig. 2a–c), was referred at age 6 weeks because of congenital cataract, minor facial anomalies, microcephaly and developmental delay. He is the first child of a 27-year-old mother and 49-year-old father. Both parents are healthy, intelligent, and non-consanguineous. Pregnancy and delivery were unremarkable. Delivery occurred at term from a cephalic presentation; birth weight was 2,620 g, length 47 cm, and OFC 32 cm. Apgar scores were 7-9-10; neonatal adaption was normal and he was discharged at age 7 days as a healthy infant with undescended testicles. At 2 weeks the mother noted no eye contact and ophthalmologic examination documented microphthalmia, microcornea (diameter 8 mm) and bilateral central congenital cataract. First physical examination at 6 weeks demonstrated microcephaly with prominent metopic suture (OFC 34 cm, below 3rd centile), short upslanting palpebral fissures, mild hypertelorism, (intercanthal distance 2.3 cm = 75th centile) short philtrum, thin lips with downturned corners of a small mouth, retrognathia, high palate, large auricles (4.5 cm = >97th centile), small penis, undescended testicles, and muscular hypotonia. Dermatoglyphics showed bilateral atypical simian creases. At 3 months he developed seizures and developmental delay became more evident. X-ray examination showed hip dysplasia bilaterally. At 1 year he was operated on for bilateral cataract and at 2 years manifested spastic diplegia. At 6 years (Fig. 3a,b) he is unable to sit, walk, speak and has some tactile and hearing contact with his mother. He is 97 cm long (<3rd centile), weighs 10 kg (<3rd centile) and his OFC is 45 cm (<3rd centile).

The first neurologic examination at age 6 weeks was unremarkable except for central hypotonia. X-ray investigation of the skull showed a small fontanelle, but no other anomaly or calcifications. Ultrasonographic

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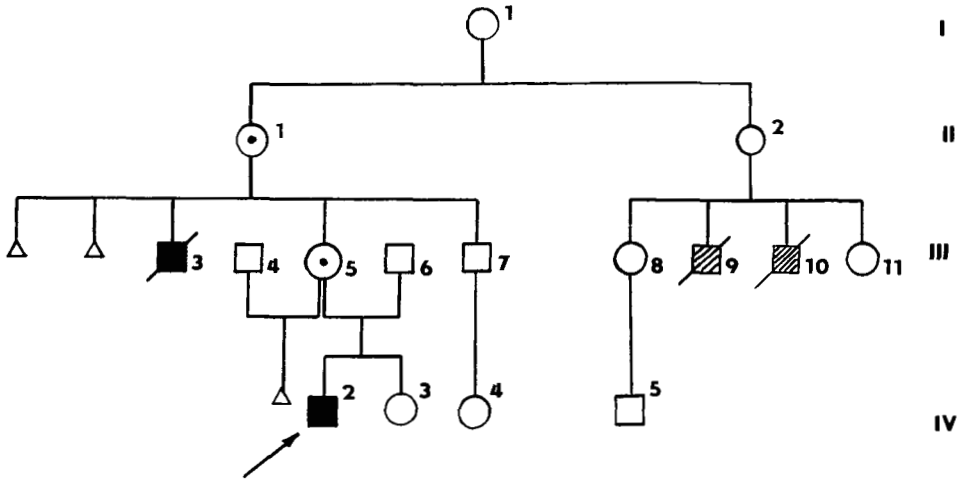

Fig. 1. Pedigree of family N documenting X-linked inheritance.

examination of the brain showed no anomalies and also showed normal heart, kidney and liver. EEG was abnormal with paroxysmal activity. Seizures occurred again at age 3 years. Spasticity started 8 months and was progressive. His skin was pale, blood count normal. Chromosomes with prophase banding were normal (46,XY) as were investigations for inborn errors of metabolism of amino acids, galactose and mucopolysaccharides. Laboratory findings were normal except for FSH and LH, which were below the normal range (FSH 0.5 IU/l, (norm 0.5–8 IU/l), LH 0.65 IU/l (norm 0.7–5 IU/l); but testosterone level was in the normal range

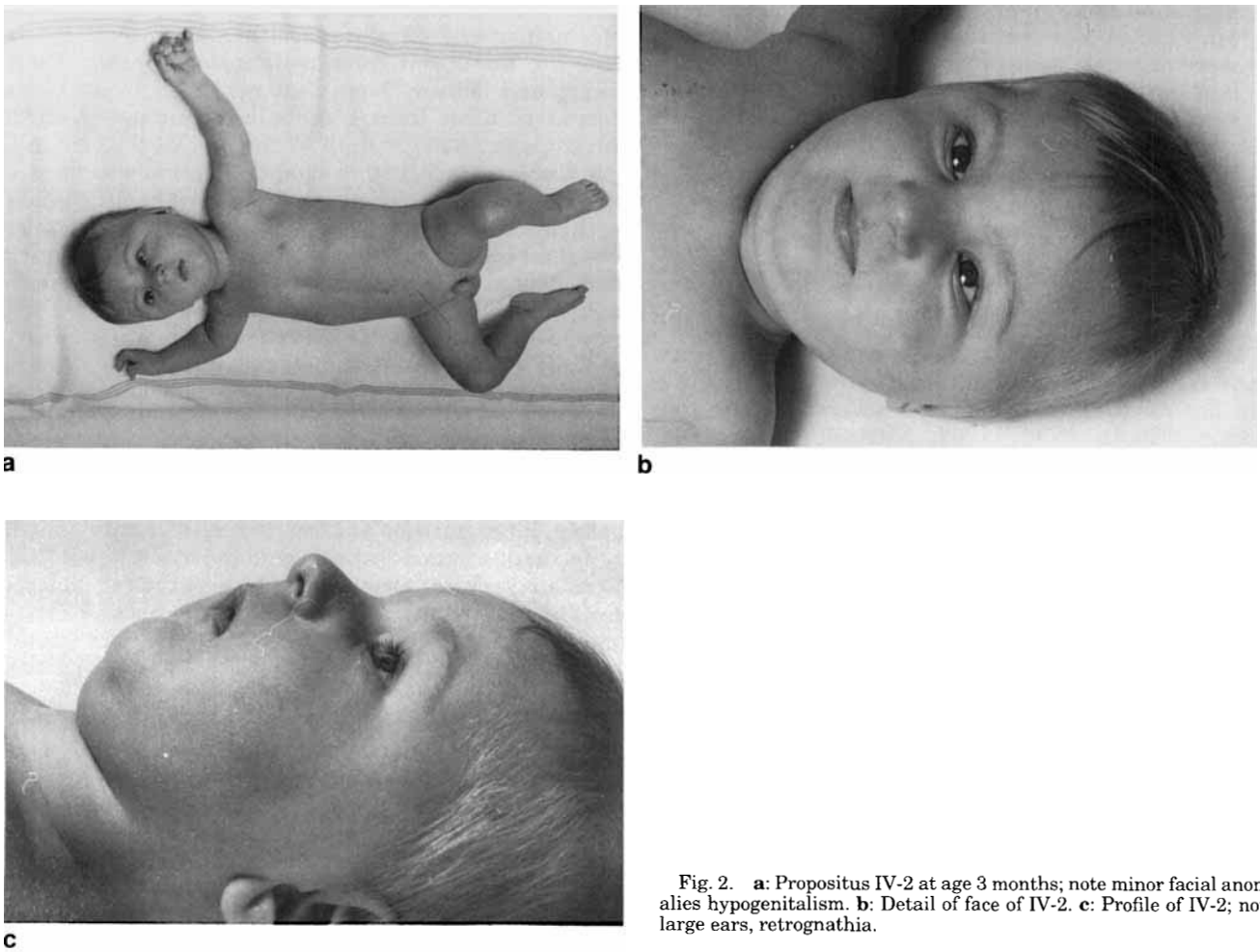

Fig. 2. **a**: Propositus IV-2 at age 3 months; note minor facial anomalies hypogenitalism. **b**: Detail of face of IV-2. **c**: Profile of IV-2; note large ears, retrognathia.

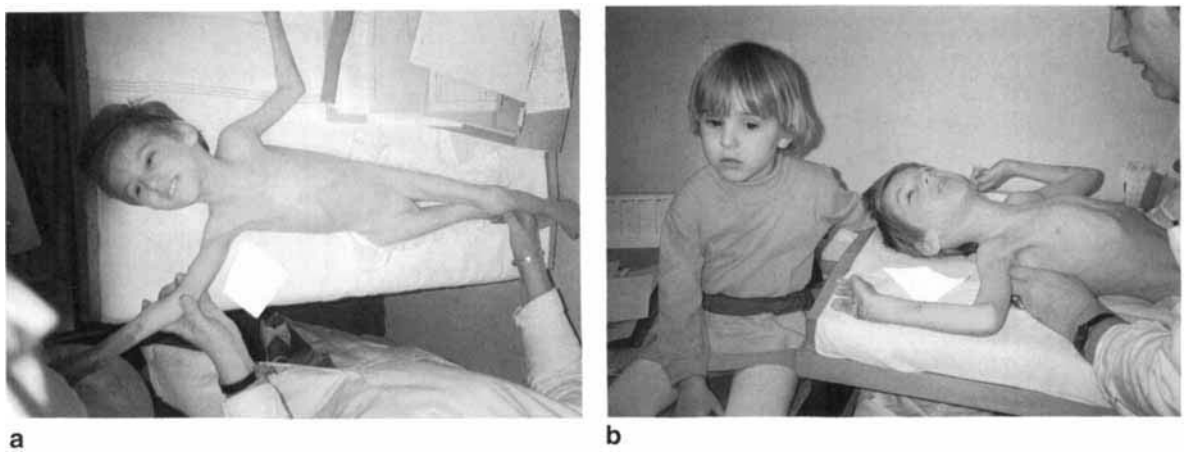

Fig. 3. **a**: Propositus IV-2 at 6 years; note hypotrophy and spasticity and (**b**) normal appearance of his younger sister.

0.66 nmol/l (norm 0.32–5.0 nmol). The parents have refused CT and MRI examination. The child (Fig. 3a) is living at home and is rarely ill. His younger sister was born 1991 at term with a birth weight of 2,950 g, length 49 cm, and is completely normal (Fig. 3b).

Patient 2

A boy, III-3 in Figure 1 (Fig. 4), was the older brother of the mother of the propositus. He died at age of 13 years in a mental institution, where he was living the last 2 years of his life. Information on him was obtained through interview of his mother, II-1, medical records and family photo documentation. He was born after two early spontaneous abortions from the third normal pregnancy at 38 weeks gestation with a birth weight of 2,100 g, length of 44 cm. He was operated on for bilateral cataract at 10 weeks when microcephaly, plagiocephaly, hypogenitalism and hypotonia were noted. His face resembles that of patient 1 (Fig. 5a,b). At age 1 year he developed seizures and progressive spasticity. He has never been able to sit, walk or speak. He died of pneumonia and autopsy finding included "dystrophy," cachexia, microcephaly, micrencephaly due to cerebral gliosis, and abdominal cryptorchidism. No other anomalies were described.

Fig. 4. Propositus's maternal uncle at age 3 months; note the similarity of facial appearence.

Patient 3

A boy, III-9, was born in 1960 from the second normal pregnancy at 38 weeks from a head presentation. Birth weight was 2,450 g, length 45 cm. Neonatal period was unremarkable except for poor suck.

He was admitted at age 4 weeks because of failure to thrive (his weight was 2,280 g and length 50 cm). Hypertelorism and epicanthal folds, large ears, retrognathia are mentioned in the medical record. The child was hypotrophic, hypotonic, had bilateral pneumonia and a heart defect was recognized as a subaortic interventricular septal defect. Cataract was not mentioned. The child died at age 6 weeks and autopsy reported hypotrophy 2,200 g, epicanthus lateris utriusque, retrognathia, hypertrophia excentrica ventriculi dextri cordis, defectus subaorticus septi interventicularis diameter 0.5×0.5 cm, kidney with cortical lobulation and undescended testicles, and bronchopneumonia. His brain weighed 370 g, OFC was 35 cm. Unfortunately no photo documentation is available. His younger brother III-10 was born in 1965 from the third normal pregnancy at term with a birth weight of 2,400 g, length 45 cm. His somatic and mental development was delayed but no medical records or photo documentation are available. The child died at home at the age of $2\frac{4}{12}$ years and autopsy was refused. The family believes he also had a heart defect.

DISCUSSION

A review of the literature and consultation with Prof. J.M. Opitz and Dr. F. Arena did not uncover any other X-linked mental retardation (XLMR) patients with microcephaly, cataract, mental and growth deficiency, or hypogonadism. In patients 1 and 2, the most likely mode of transmission is X-linked inheritance, probably 2 other maternal male relatives were similarly affected. No chromosomal or metabolic disorders were found in the propositus. The disorder represents a progressive neurological handicap, with prenatal onset of growth retardation. Clinical findings of our patients are summarized in Table I.

Some syndromes of microcephaly, congenital cataract, mental and growth deficiency, congenital hypoto-

Fig. 5. **a**: Maternal uncle III-3 at the age of 6 years; note spasticity and hypotrophy. **b**: Maternal uncle III-3 at age 12 years; note progression of hypotrophy and spasticity.

TABLE I. Summary of Clinical Findings

	IV-2 TN	III-3 DG	III-9 VH	III-10 JH
Birth at gestational age	40	38	38	40
Hypotrophy	+	+	+	+
Small for gestational age	2,620/47	2,100/45	2,450/45	2,400/45
Microcephaly	+	+	+	?
Mental retardation	+	+	?	+
Congenital cataract	+	+	?	?
Hypogonadism	+	+	+	?
Cryptorchidism	+	+	+	?
Congenital hypotonia	+	?	+	?
Seizures	+	+	Died age 6 weeks	?
Progressive spasticity	+	+	−	?
Hypertelorism	+	+	+	?
Epicanthal folds	+	+	+	?
Large ears	+	+	+	?
High palate	+	?	?	?
Retrognathia	+	+	+	?
Congenital heart defect	−	−	+	?

TABLE II. Differential Diagnosis

Clinical findings	Our patients	Lowe [1960]	Pfeiffer and Steffann [1985]	Seemanová et al. [1973]	Paine [1960]	Börjeson et al. [1962]	Juberg and Marsidi [1980]
Small for gestational age	+	±	?	−	+	−	?
Microcephaly congenital	+	±	−	+	+	+	+
Congenital cataract	+	−	+	−	−	−	±
Growth retardation	+	±	−	+	+	±	+
Mental retardation	+	+	−	+	+	+	+
Hypogonadism	+	±	−	±	?	+	+
Retrognathia	+	−	−	−	?	±	−
Seizures	+	+	−	+	+	+	?
Progressive spasticity	+	−	−	+	+	−	?
Never walked	+	−	−	+	±	−	?
Deafness	−	−	−	∓	−	−	+

nia, hypogonadism were excluded on the basis of inheritance, such as Smith-Lemli-Opitz syndrome or Martsolf syndrome or oculopalatocerebral syndrome. Differential diagnosis of X-linked syndromes is summarized in Table II. Some other X-linked syndromes with microcephaly, cataract and hypogonadism and severe mental retardation could be excluded by finding of a normal amino acid pattern (Lowe syndrome), by progression of neurological disorder and absence of severe microcephaly [Pfeiffer, 1985]. Absence of cataract makes Paine syndrome, Seemanová I. syndrome, Börjeson-Forsmann-Lehmann syndrome, and Juberg-Marsidi syndromes unlikely. Thus, this entity may represent a new syndrome.

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